Physiological Adaptive Radiotherapy

James Balter
Yue Cao
University of Michigan

No conflicts exist

Background

• While geometric and biological adaptation have some benefit, individual patients have tumors and normal tissues that respond differentially to the same therapy
• Probes that more directly predict the response of individual patients to treatment may enhance the benefit of therapy individualization

Examples of physiological probes

• Blood tests
  – ICG, TGFβ
• Imaging surrogates
  – Metabolism (FDG)
  – Perfusion (DCE, MAA)
  – Ventilation
  – Diffusion
  – Diffusion Tensor
  – Spectroscopy
Dose “painting”

- Theory: Tumors have differential responses that can be spatially mapped.
- Adjusting the dose distribution to provide heterogeneity that relates to the (imaged) distribution of mapped surrogate markers can improve local control, and potentially survival.
- Challenges:
  - Spatial resolution
  - Signal reproducibility
  - Sensitivity
  - Mapping to physical patient
  - Achieving sufficient differentiation to be biologically relevant.

Duprez et al – dose painting by the numbers

- Direct formula relating SUV to local dose increase.
- PET-directed dose painting performed twice over the treatment course.
- Remaining dose via “standard” IMRT.


Duprez et al – dose versus PET intensity

\[ D_I = D_{low} + \frac{I - I_{low}}{I_{high} - I_{low}}(D_{high} - D_{low}) \]

- \( I_{high} \) – 95% of max on PET
- \( I_{low} \) – 25% of \( I_{high} \).
Adaptive dose painting - toxicity

FDG PET-based dose painting has been demonstrated, in clinical trials to be:

- 21% 1. Safer than conventional IMRT
- 21% 2. More effective than conventional IMRT
- 19% 3. Practical to deliver, but without published evidence of improved local control
- 19% 4. Practical to deliver, but without published evidence of safety
- 19% 5. Impractical due to increased toxicity with no evidence of benefit

Table 1. Incidence of acute toxicity observed at dose level 1 and 2

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dose level 1</th>
<th>Dose level 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Myelitis</td>
<td>—</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Myelitis</td>
<td>4 (20%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6 (30%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Myelitis</td>
<td>6 (30%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>6 (30%)</td>
<td>6 (30%)</td>
</tr>
</tbody>
</table>

- Dose was escalated within GTV safely
- FDG-aided dose painting did not significantly increase toxicity beyond conventional doses
- No improvement realized on tumor control

Limited sensitivity of PET

Christian et. al – Simulated PET images from Autoradiographs
- included effects of blurring, voxel sampling
- showed decreased sensitivity of PET image relative to underlying signals

Factors that limit PET as a Primary tool for dose painting include:

- 1. Excess radiation dose from imaging
- 2. Limited sensitivity
- 3. Lack of availability of PET scanners
- 4. Cost of imaging
- 5. Spatial distortion

Answer: 2.

Biomarker-based early assessment

- Deliver enough dose to manifest patient-specific early effects
- Alter decisions for remaining treatment based on observations:
  - Rearrange dose to:
    - Lower toxicity risk
    - Locally boost non-responding tumor
  - Lower/Raise overall dose based on likelihood of overall response/risk

RTOG 1106

- Based on the observation that FDG-avid regions of lung tumors shrink
- Initial PTV receives intended dose (up to lung dose tolerance)
- Boost volume based on FDG-avid volume during treatment (dose based on screening plan bin)

Spring Kong, UM
RTOG 1106 Schema

SCREENING PLAN
- to determine Mean Lung Dose & Tx Dose Bin (74 Gy to 95% PTV)

RANDOMIZED RATIONAZION (BASED LUNG Dose & TUMOR VOLUME)

ARM 1: CONCURRENT CHEMO-RT
- RT to 50 Gy (2 Gy/Fx)
- Carboplatin/Paclitaxel Weekly

ARM 2: CONCURRENT CHEMO-RT
- RT to 47.5-49.5 Gy (variable Gy/Fx)
- Carboplatin/Paclitaxel Weekly

DURING-TX FDG-PET/CT IMAGING

ARM 1: CONTINUE RT
- Same RT plan to 60 Gy total (30 Fx)

ARM 2: ADAPTIVE RT
- Based on during-tx FDG-PET RT up to 85.5 Gy individualized by MLD

CONSOLIDATIVE CHEMOTHERAPY

Individualized Dose Prescription

<table>
<thead>
<tr>
<th>Initial Plan</th>
<th>Physical</th>
<th># Fraction</th>
<th>Total</th>
<th>Prescription</th>
<th>Physical</th>
<th># Fraction</th>
<th>Total</th>
<th>Prescription</th>
<th>Physical</th>
<th># Fraction</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1 PTV</td>
<td>14.0</td>
<td>2.85</td>
<td>20</td>
<td>49.7</td>
<td>3.0</td>
<td>36.9</td>
<td>11</td>
<td>84.6</td>
<td>2.95</td>
<td>20</td>
<td>49.7</td>
</tr>
<tr>
<td>Arm 2 PTV</td>
<td>14.0</td>
<td>2.85</td>
<td>20</td>
<td>49.7</td>
<td>3.0</td>
<td>36.9</td>
<td>11</td>
<td>84.6</td>
<td>2.95</td>
<td>20</td>
<td>49.7</td>
</tr>
<tr>
<td>Arm 1 PTV</td>
<td>14.0</td>
<td>2.85</td>
<td>20</td>
<td>49.7</td>
<td>3.0</td>
<td>36.9</td>
<td>11</td>
<td>84.6</td>
<td>2.95</td>
<td>20</td>
<td>49.7</td>
</tr>
<tr>
<td>Arm 2 PTV</td>
<td>14.0</td>
<td>2.85</td>
<td>20</td>
<td>49.7</td>
<td>3.0</td>
<td>36.9</td>
<td>11</td>
<td>84.6</td>
<td>2.95</td>
<td>20</td>
<td>49.7</td>
</tr>
</tbody>
</table>

This is the Rx for Arm 2 Initial Plan

Spring Kong, UM
Treatment Targets for Arm 2

30 daily fractions, 2.2-4.25 Gy daily fractions

CT1GTV = EX1GTV + IN1GTV + PET1MTV
CT1CTV = CT1GTV + 0.5 cm
CT1GTV = CT1GTV + at least 0.5 cm

Targets for the 1st plan
PET2PTV = PET2MTV + 0.5 cm
CT1CTV = CT1CTV + 0.5 cm
CT1PTV = CT1PTV + 0.5 cm

Targets for adaptive plan
PET2PTV = PET2MTV + 0.5 cm
CT1GTV = CT1GTV + at least 0.5 cm

30 daily fractions, 2.2-4.25 Gy daily fractions

Spring Kong, UM

Adaptive Plan Targets

CT2PTV (>70 Gy Composite)

Spring Kong, UM

Persistent Low Blood Volume as a boost volume for HNC?
• Prognostic Values of Pre Tx tumor BV and perfusion
  • Outcome from RT (Hermans 1997 & 2003)
  • Response to induction chemotherapy (Zima 2007)
  • Better perfused HNC → better response to CT & RT

Regions of persistent low blood volume within initial PTV may present a target for integrated boost

Pre RT

2 weeks after the start of RT
High Cerebral Blood Volume (CBV) in High-Grade Gliomas – local boost volume?

\[ fTV \text{ w High-CBV } < 0.07 \]
\[ fTV \text{ w High-CBV } > 0.07 \]

P = 0.002

Cao, IJROPB, 2006

---

Early CBV Changes During RT

Pt A
Decrease
Better OS

Pt B
Little Change
Worse OS

Y Cao, UM

---

TBV change predictive of LF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-RT</th>
<th>% Change (w 2 – pre-RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LC (n = 9)</td>
<td>8.5 (1.3–17.5)</td>
<td>5.1 (−0.6 to 13.2)</td>
</tr>
<tr>
<td>LF (n = 4)</td>
<td>10.2 (8.0–13.0)</td>
<td>1.0 (−1.7 to 1.6)</td>
</tr>
<tr>
<td>RC (n = 10)</td>
<td>9.3 (4.6–16.0)</td>
<td>0.2 (−4.6 to 10.0)</td>
</tr>
<tr>
<td>RF (n = 2)</td>
<td>10.1 (5.9–14.3)</td>
<td>−3.1 (−4.5 to −1.8)</td>
</tr>
</tbody>
</table>

Normal tissue sparing

- Ventilation/perfusion for assessing normal lung function distribution for treatment planning/adaptation
- Perfusion for liver toxicity prediction/dose modification

Pre-treatment:
RT planning with functional lung sparing based on perfusion SPECT

Liver adaptive radiotherapy

- RILD (liver toxicity) includes venous occlusion as a noted symptom
- Dynamic contrast-enhanced (DCE) imaging and analysis of venous perfusion has been hypothesized as a mechanism for customizing treatment to limit toxicity while maximizing tumor dose
DCE MRI and CT - Early Assessment of Venous perfusion changes as a predictor of local damage

Cao Y et al, Medical Physics 2007

Prior to RT

After 45 Gy

30 fx of 1.5 Gy/fx twice daily

DCE CT study - Methods

• Eleven patients with unresectable intrahepatic cancer
  – 1 with hepatocellular carcinoma, 5 with cholangiocarcinoma, and 5 with colorectal carcinoma metastatic to the liver
• 3D conformal RT
  – 1.5 Gy/fraction b.i.d.
  – Median dose 67.5 Gy (range 48–78 Gy)
  – Concurrent continuous infusion hepatic artery floxuridine (FUDR) as a radiation sensitizer for the first 4 weeks of RT
• CT Liver perfusion protocol
  – Pre RT, after 15 and 30 Fx, and 1 month after RT
• Overall liver function assessment
  – indocyanine extraction
  – Pre RT, after 15 and 30 Fx, and 1 month after RT

Results: Individual Perfusion Dose Response

Slope: reduction in perfusion caused by every Gy
Intercept with x axis: critical dose resulting in undetectable venous perfusion

Cao, Int J Rad Onc Biol Phys, 2007
Evaluation of Overall Liver Function

Indocyanine green: independent measure of overall liver function

Results: Correlation of venous perfusion with Overall Liver Function

The mean perfusion in the functional liver volume, but not the mean liver dose, correlates with the half life time of ICG clearance.

Normal liver sparing based on DCE perfusion is based on the premise that

23% 1. Venous occlusion is a symptom of RILD
21% 2. DCE imaging is easy to perform in the liver
18% 3. Hypervascularity is a symptom of radiation injury
21% 4. No other imaging seems to work
18% 5. The biological model of radiation dose versus perfusion damage has been thoroughly tested
Answer: 1.


---

Functional Bone Marrow Sparing (UCSD)

- LK Mell et al (UCSD). (JCO 28(15)suppl, 2010: e13570)
- MRI mapping of functional bone marrow supported dose re-organization for sparing blood formation in pelvic RT

---

Serial IDEAL Fat Fraction Maps in a Cervical Cancer Patient Undergoing Chemoradiation

Pre-Treatment  | Mid-Treatment  | Post-Treatment

Loren Mell, UCSD
Evidence to date

• Some individualized therapy trials are underway
• Little direct clinical evidence to date
  – Ghent –HN dose painting – evidence to date is that
dose can be modified safely
  – Kong – lung dose adaptation – evidence to date is that
local boosting can be achieved safely respecting
normal tissue limits
  – No substantial statistical evidence to date of:
    • Improved local control
    • Improved normal tissue sparing at same local control

Current evidence clearly shows that
physiological adaptation improves:

1. Local control for gliomas
21%
2. Survival for head and neck cancer
21%
3. Toxicity for intrahepatic radiotherapy
21%
4. Toxicity for intrathoracic tumors
19%
5. None of the above
20%
Answer: 5.


Technical challenges

- Image-based maps need to be applied to the physical patient
- Dose accumulation further requires accurate mapping
- Shrinking tumors require assumptions about dose addition

Current solutions for dose accumulation

- Duprez – local rigid image registration
- RTOG 1106 – Rigid alignment biased towards local skeletal alignment in vicinity of PTV
Summary

• Physiological adaptation is emerging as a tool in clinical trials
• Preliminary evidence indicates a potential role for such adaptation
• Evidence to date has indicated the potential for dose modification, but has not yet proven improvement in local control, nor equivalent control at reduced toxicity

Acknowledgements

• Fengming Kong
• Randall Ten Haken
• Martha Matuszak
• Lauren Mell (UCSD)